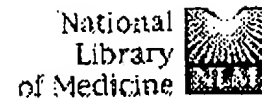


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Fusion of a signal sequence to the interleukin-1 beta gene directs the protein from cytoplasmic accumulation to extracellular release.

Wingren AG, Bjorkdahl O, Labuda T, Bjork L, Andersson U, Gullberg U, Hedlund G, Sjogren HO, Kalland T, Widegren B, Dohlsten M.

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Interleukin (IL)-1 differs from most other cytokines by the lack of a signal sequence, which results in the retention of the immature proform intracellularly (i.e.). Several cell types have the capacity to produce IL-1, but release has been shown to be restricted predominantly to monocytes/macrophages and associated with apoptosis of the producer cell. These features have limited the studies on IL-1 in early T cell-APC interactions. To develop a model for studying the biological effects of IL-1 beta release during long-lasting immune responses, we have established cells transfected with IL-1 beta cDNA constructs. To construct a hybrid gene for IL-1 beta release, the signal sequence from the related IL-1 receptor antagonist was fused to the gene encoding the 17-kDa mature form of IL-1 beta. A murine fibroblast cell line was transduced with retroviral technique and analyzed for the expression of human IL-1 beta, with or without a signal sequence (ssIL-1 beta and IL-1 beta, respectively). The fibroblasts transduced with either IL-1 beta or ssIL-1 beta expressed similar levels of human IL-1 beta mRNA. High levels of IL-1 bioactivity were recorded in freeze-thaw extracts from cells expressing the IL-1 beta protein i.e., and in supernatants of ssIL-1 beta-transduced cells, which indicates that the initial formation of a proform of IL-1 beta is not required for correct folding of the protein. Treatment of ssIL-1 beta-transduced cells with Brefeldin A (BFA), an inhibitor of protein transport in the endoplasmic reticulum, induced accumulation of the protein i.e. BFA treatment did not affect IL-1 beta-transduced cells, while lipopolysaccharide-activated human monocytes increased the secretion of IL-1 beta. Cytoplasmic staining of single cells demonstrated that expression of the ssIL-1 beta gene directed the protein to a perinuclear Golgi-like compartment, whereas cells transduced with IL-1 beta cDNA showed a diffuse cytoplasmic distribution pattern. Secretion of IL-1 beta from human monocytes was under certain conditions accompanied by cell death. In contrast, in the fibroblast cell line transduced to secrete IL-1 beta, no accompanying cell death could be detected. Gene targeting of IL-1 to the secretory or cytoplasmic pathway may be useful for elucidating the role of IL-1 in T cell-APC interactions, avoiding cell death of the producer cells.

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